



An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 1/21/2016
LAST REVIEW DATE: 8/19/2021
LAST CRITERIA REVISION DATE: 8/19/2021
ARCHIVE DATE:

ENTRESTO™ (sacubitril and valsartan) VERQUVO™ (vericiguat)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the [request form](#) in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**



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Criteria:

Entresto (sacubitril and valsartan)

➤ **Criteria for initial therapy:** Entresto (sacubitril and valsartan) is considered *medically necessary* and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Cardiologist
2. There is a confirmed diagnosis of symptomatic heart failure (New York Heart Association or Ross Class II-IV)
3. Individual is **ONE** of the following:
 - a. Adult (18 years of age or older) and **BOTH** of the following:
 - i. Left ventricular ejection fraction is $\leq 40\%$ **or** has left ventricular ejection fraction is $\geq 45\%$ with structural heart disease (i.e., left atrial enlargement (LAE), left ventricular hypertrophy (LVH))
 - ii. Will be used in combination with an evidence-based maximally tolerated dose of other therapies for heart failure such as beta-blocker, aldosterone antagonist or mineralocorticoid receptor antagonist in selected individuals where clinically appropriate for age and condition (unless experienced previous failure, contraindicated, intolerance, or is not indicated)
 - b. Pediatric (1 year of age or older) and **BOTH** of the following:
 - i. Left ventricular ejection fraction is $\leq 40\%$ **or** has a fractional shortening of $\leq 20\%$
 - ii. On chronic heart therapy which will be continued, unless newly diagnosed
 - iii. Angiotensin converting enzyme inhibitors and angiotensin receptor blocking agents will be stopped prior to use of Entresto (sacubitril and valsartan)
4. The baseline plasma B-type natriuretic peptide level (BNP) or plasma N-terminal pro-brain natriuretic peptide (NTproBNP) level is elevated
5. There are no significant interacting drugs
6. There are **NO** FDA-label contraindications, such as:
 - a. History of angioedema to previous ACE inhibitor therapy
 - b. History of angioedema to previous ARB therapy
 - c. Simultaneous use with ACE inhibitor therapy
 - d. Use within 36 hours of an ACE inhibitor therapy
 - e. Simultaneous use with aliskiren (brand Tekturna or a generic) in patients with diabetes
 - f. Hypersensitivity to any component

Initial approval duration:

- If the individual has **NOT** been seen by a cardiologist within 6 months **AND** the request is for initial **OR** continuation of therapy: 60-day transition of care period to permit ample time to be seen by a cardiologist



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- If seen by a cardiologist: 12 months
- **Criteria for continuation of coverage (renewal request):** Entresto is considered *medically necessary* and will be approved with documentation of **ALL** of the following:
 1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Cardiologist at least yearly
 2. Individual's condition responded while on therapy
 - a. Response is defined as **TWO** of the following:
 - i. There has been a reduction in hospitalizations for heart failure in the last 12 months while on therapy compared to baseline or compared to previous year
 - ii. Achieves and maintains a reduction in B-type natriuretic peptide level (BNP) or N-terminal pro-BNP level
 - iii. There is no evidence of disease progression, defined as **either**:
 1. Worsening signs and symptoms of heart failure that requires intensification of heart failure therapy such as hospitalization with or without an intensive care unit stay
 2. Worsening NYHA/Ross functional class
 3. Individual has been adherent with the medication
 4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use:
 - a. Contraindications as listed in the criteria Initial therapy section
 - b. Significant adverse effect such as:
 - i. Angioedema
 - ii. Untreated hyperkalemia
 - iii. Progressive and/or significant deterioration of kidney function
 5. There are no significant interacting drugs

Renewal duration: 12 months

Verquvo (vericiguat)

Criteria:

- **Criteria for initial therapy:** Verquvo (vericiguat) is considered *medically necessary* and will be approved when **ALL** of the following criteria are met:
 1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Cardiologist



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2. Individual is 18 years of age or older
3. A confirmed diagnosis of symptomatic worsening chronic heart failure (New York Heart Association Class II-IV)
4. Worsening heart failure defined as **ONE** of the following:
 - a. History of previous heart failure hospitalization within the last 6 months
 - b. Out-patient intravenous diuretic for heart failure (without hospitalization) within previous 3 months
5. Individual has been using 3 or more of the following heart failure medications:
 - a. Diuretic
 - b. Beta-blocker such as bisoprolol, carvedilol, or sustained release metoprolol
 - c. Any angiotensin system inhibitor such as:
 - i. Angiotensin converting enzyme inhibitor (ACEI)
 - ii. Angiotensin receptor blocker (ARB)
 - iii. Angiotensin receptor-neprilysin inhibitor (ARNI)
 - iv. Mineralocorticoid receptor antagonist
 - d. Hydralazine plus nitrate
 - e. Corlanor (ivabradine)
 - f. Farxiga (dapagliflozin) or Jardiance (empagliflozin)
6. **ALL** of the following **baseline tests** have been completed before initiation of treatment with continued monitoring as clinically appropriate:
 - a. A negative pregnancy test in a woman of childbearing potential
7. Ejection fraction less than 45% assessed within the previous 12 months
8. There is documentation of an elevated brain natriuretic peptide (BNP) or NT-proBNP level within the previous 30 days
9. Systolic blood pressure is at least 100 mmHg or has no symptoms of hypotension
10. Will not be using long-acting nitrates such as isosorbide dinitrate, isosorbide 5-mononitrate, transdermal nitroglycerin, other similar agents
11. Will not be used in individuals with estimated glomerular filtration rate (eGFR) less than 15 mL/min/1.73m² or on dialysis
12. Will not be used in individuals with severe hepatic impairment (Child-Pugh Class C)
13. There are no significant interacting drugs
14. There are **NO** FDA-label contraindications, such as:
 - a. Concurrent use with other soluble guanylate cyclase stimulators such as Adempas (riociguat)



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ENTRESTO™ (sacubitril and valsartan) VERQUVO™ (vericiguat)

- b. Concurrent use with phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil, tadalafil, vardenafil
- c. Woman of child bearing potential who is pregnant

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Verquvo (vericiguat) is considered *medically necessary* and will be approved when **ALL** of the following criteria are met:
1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Cardiologist
 2. Individual's condition has responded while on therapy.
 - a. Response is defined as **TWO** of the following:
 - i. There has been a reduction in hospitalizations for heart failure in the last 12 months while on therapy compared to baseline or compared to previous year
 - ii. Achieves and maintains a reduction in B-type natriuretic peptide level (BNP) or N-terminal pro-BNP level
 - iii. There is no evidence of disease progression, defined as **either**:
 1. Worsening signs and symptoms of heart failure that requires intensification of heart failure therapy such as hospitalization with or without an intensive care unit stay
 2. Worsening NYHA functional class
 3. Individual has been adherent with the medication
 4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
 - a. Contraindications as listed in the criteria for initial therapy section
 - b. Significant adverse effect such as:
 - i. Symptomatic hypotension
 - ii. Syncope
 5. There are no significant interacting drugs

Renewal duration: 12 months

Description:

Ernesto (sacubitril and valsartan) is a combination of the neprilysin inhibitor, sacubitril, and the angiotensin II receptor blocker (ARB), valsartan. In adults, it is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure. The benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. Ernesto (sacubitril and valsartan) is also



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ENTRESTO™ (sacubitril and valsartan) **VERQUVO™ (vericiguat)**

indicated for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. It reduces NT-proBNP and is expected to improve cardiovascular outcomes.

Verquvo (vericiguat) is indicated to reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45%.

Heart failure (HF) is a complex chronic progressive clinical syndrome in which the heart muscle is unable to pump enough blood to meet the body's needs. Diagnosis is made based on a careful history and physical examination. Mortality rate is high, approximately 50% of patients die within five years of diagnosis despite the availability of medications with proven mortality benefit.

NYHA categorizes HF into four classes depending on a patient's functional status, ranging from no limitation in physical activity (Class I), to an inability to carry out any physical activity without discomfort (Class IV). Treatment options for NYHA class II to IV heart failure with reduced ejection fraction include ACE inhibitors or ARB, angiotensin receptor neprilysin inhibitors (ARNIs), beta-blockers (bisoprolol, carvedilol, or sustained release metoprolol), and aldosterone antagonists (eplerenone or spironolactone). Loop diuretics and vasodilators (hydralazine with isosorbide dinitrate) are added depending on symptoms and ethnicity. Digoxin may also be used in certain circumstances.

According to current guidelines, beta-blockers and ACE inhibitors, ARBs, or ARNIs are the cornerstone of the management of HF and have been shown in randomized controlled studies to reduce HF associated morbidity and mortality. Entresto (sacubitril and valsartan) has not been evaluated for monotherapy for heart failure with reduced ejection fraction, for the treatment of heart failure with preserved ejection fraction, or in the treatment of hypertension.

Signs and symptoms of HF are a result of compensatory mechanisms involved in an effort to restore cardiac output. Neurohumoral adaptations include activation of the renin-angiotensin-aldosterone (RAAS) and the sympathetic adrenergic nervous system, increased release of vasopressin (antidiuretic hormone) and various natriuretic peptides. The net effect of the neurohumoral response is to cause vasoconstriction and to increase blood volume. Over time, these compensatory changes can worsen heart failure. Prolonged HF also leads to a depletion of several endogenous vasoactive peptides are involved in vasodilation, natriuresis, diuresis, and inhibition of pathologic growth and fibrosis.

Vasoactive peptides include atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), bradykinin, adrenomedullin, substance-P, vasoactive intestinal peptide, and calcitonin gene regulated peptide. Release into the circulation is stimulated by sodium overload, increase in extracellular volume, distension of auricles and ventricles. Their plasma half-life is very short as they are inactivated by neprilysin which degrades these to inactive products. Neprilysin expression is upregulated in heart failure patients. Inhibition of neprilysin increases the levels of vasoactive peptides, countering the neurohumoral overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling.



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VERQUVO™ (vericiguat)

Assays for BNP (B-type natriuretic peptide) and NTproBNP (N-terminal pro-B-type natriuretic peptide), are both natriuretic peptide biomarkers, have been used increasingly to establish the presence and severity of heart failure. A substantial evidence base exists that supports the use of natriuretic peptide biomarkers to assist in the diagnosis or exclusion of heart failure as a cause of symptoms. Current clinical practice guidelines give a Class I recommendation to measure BNP or NT-proBNP to support a clinical diagnosis of heart failure, to assess disease severity, or to establish prognosis.

Angiotensin II that interacts with its AT-1 receptor causes vasoconstriction, sodium and water retention, and fibrosis/hypertrophy. Use of an ARB prevents these actions of angiotensin II.

Sacubitril is a prodrug that is converted to its active metabolite which inhibits neutral endopeptidase (neprilysin). Valsartan inhibits the effects of angiotensin II by selectively blocking at the angiotensin (AT)-1 receptor and it inhibits angiotensin II-dependent aldosterone release.

Verquvo (vericiguat) is a stimulator of soluble guanylate cyclase (sGC), an important enzyme in the nitric oxide (NO) signaling pathway. When NO binds to sGC, the enzyme catalyzes the synthesis of intracellular cyclic guanosine monophosphate (cGMP), a second messenger that plays a role in the regulation of vascular tone, cardiac contractility, and cardiac remodeling. Heart failure is associated with impaired synthesis of NO and decreased activity of sGC, which may contribute to myocardial and vascular dysfunction. By directly stimulating sGC, independently of and synergistically with NO, vericiguat augments levels of intracellular cGMP, leading to smooth muscle relaxation and vasodilation.

Definitions:

New York Heart Association (NYHA)/Ross Heart Failure Classification:

	Adult – NYHA Heart Failure	Infant and Children – Ross Heart Failure
Class I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc	No limitations or symptoms
Class II	Mild symptoms mild dyspnea and/or angina, fatigue, palpitations, and slight limitation during ordinary activity or moderate exercising but not during rest	Infant: mild tachypnea or diaphoresis with feeding; older child: mild to moderate dyspnea on exertion; no growth failure
Class III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20-100 m) or minimal exertion that interfere with normal daily activity, comfortable only at rest	Infant: marked tachycardia or diaphoresis with feeding, prolonged feeding times; older child: marked dyspnea on exertion; growth failure from CHF
Class IV	Severe limitations, unable to carry out any physical activity because experiences symptoms even while at rest that worsen with any exertion, mostly bedbound patients	Symptomatic at rest with tachypnea, retractions, grunting, or diaphoresis



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American College of Cardiology (ACC)/American Heart Association (AHA) Stages of HF:

- Stage A: At high risk for HF but without structural heart disease or symptoms of HF
- Stage B: Structural heart disease but without signs or symptoms of HF
- Stage C: Structural heart disease with prior or current symptoms of HF
- Stage D: Refractory HF requiring specialized interventions

Fractional Shortening:

The reduction of the length of the end-diastolic diameter that occurs by the end of systole. Using the M-Mode the parameters left ventricular end-systolic diameter (LVESD) and the left ventricular end-diastolic diameter (LVEDD) are derived. Using the formula: $(LVEDD - LVESD / LVEDD) \times 100$, the percentage of size differences of the left ventricle as a factor of how well the left ventricle is contracting is calculated. Like the ejection fraction, this is a measure of the heart's muscular contractility. If the diameter fails to shorten by at least 28%, the efficiency of the heart in ejecting blood is impaired. Normal range is 26–45%, Mild is 20–25%, Moderate is 15–19%, and Severe is < 15%. Using 2D measurement, the normal fractional shortening is > 18%.

Resources:

Entresto (secubitril and valsartan) product information, revised by Novartis Pharmaceuticals Corporation 10-2019, at DailyMed <http://dailymed.nlm.nih.gov>. Accessed February 06, 2021.

Verquvo (vericiguat) product information, revised by Merck Sharp and Dohme Corp. 01-2021, at DailyMed <http://dailymed.nlm.nih.gov>. Accessed February 01, 2021.

Colucci WS. Overview of the management of heart failure with reduced ejection fraction in adults. In: UpToDate, Gottlieb SS, Dardas TF (Eds), UpToDate, Waltham MA.: UpToDate Inc. <http://uptodate.com>. Accessed on February 6, 2021.

Meyer TE. Initial pharmacologic therapy of heart failure with reduced ejection fraction in adults. In: UpToDate, Gottlieb SS, Dardas TF (Eds), UpToDate, Waltham MA.: UpToDate Inc. <http://uptodate.com>. Accessed on February 6, 2021.

Colucci WS. Secondary pharmacologic therapy in heart failure with reduced ejection fraction in adults. In: UpToDate, Gottlieb SS, Dardas TF (Eds), UpToDate, Waltham MA.: UpToDate Inc. <http://uptodate.com>. Accessed on February 6, 2021.

Borlaug BA, Colucci WS. Treatment and prognosis of heart failure with preserved ejection fraction. In: UpToDate, Gottlieb SS, Dardas TF (Eds), UpToDate, Waltham MA.: UpToDate Inc. <http://uptodate.com>. Accessed on June 21, 2021.

Armstrong PW, Pieske B, Anstrom KJ, et al; VICTORIA Study Group. Vericiguat in patients with heart failure and reduced ejection fraction. NEJM 2020;382(20):1883-1893. doi:10.1056/NEJMoa1915928. Accessed February 6, 2021.